REMARKS

The Office Action and the cited and applied references have been carefully studied. No claim is allowed. Claims 3, 5-11, 17, 18 and 22-31 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Regarding the 35 U.S.C. §103(a) obviousness rejection over the cited and applied Prestwich, Akima and Gallardy references, applicants wish to add to the comments on synergistic effects of the presently claimed invention, as supported by Figures 6 and 7 of the present application and appearing on page 9, fist full paragraph, of the amendment filed December 9, 2006. The present specification at page 61, line 11 to page 62, line 8, teaches that the results in Figs. 6 and 7 demonstrate that the conjugate recited in the present claims can be retained at the joint cavity for a long period of time. Thus, it is clear from the gelatinase B inhibiting activity of the synovial fluid (Fig. 7) and the amount of the therapeutic agent remaining in the joint 17 hours after administration that the conjugate recited in the present claims can be significantly retained for a long period of the

time in contrast to a therapeutic agent for joint diseases and HA, used alone or in combination.

It would be well recognized and understood by those of ordinary skill in the art reading the present specification that the "retainability" of the HA-drug conjugate means that (1) the HA-drug conjugate recited in the present claims is retained at a joint cavity without being dissociated or decomposed in order to exhibit their synergistic effects, and (2) the HA-drug conjugate is retained at the joint cavity for a long period of time. This has the advantageous effect of being able to treat joint diseases with less frequency of administration of the drug. Prestwich does not suggest at all the retainability of the HA-drug conjugate in which the HA and the drug are kept joined to each other via the spacer without being dissociated or decomposed at the target site (i.e., a joint cavity) for a long period of time. Accordingly, it cannot be expected from Prestwich, even in combination with the secondary Akima and Gallardy references, which do not satisfy the deficiencies of Prestwich, that the conjugate recited in the present claims has better efficacy and retainability as a therapeutic agent for joint diseases or HA used alone or in combination, as evidenced by the comparative results shown in Figs. 6-7.

Furthermore, Prestwich discloses at column 14, lines 38-45, that the cross-linked hyaluronate derivatives are particularly preferred over native hyaluronic acid and that the cross-linked hyaluronate derivatives are further preferred merely as a vehicle/carrier. The cross-linked hyaluronate derivatives are disclosed in the previous paragraph at column 14 of Prestwich with regard to forming hydrogels of the hydrazido-functionalized HA. It is apparent from column 7, lines 17-25, that it is the pendent group, i.e., the hydrazido group, that allows cross-linking of HA. Thus, one of ordinary skill in the art reading the Prestwich reference would consider the hydrazido pendent group to be critical to the anti-arthritis utility because the HA must first be cross-linked into a hydrogel by means of this hydrazido group before it could be used for this utility. Therefore, there would certainly be no motivation to substitute the amido conjugates of Akima for the treatment of arthritis, as the amido conjugation leaves no moiety free for cross-linking into a hydrogel.

The present specification at page 7, lines 7-25, further teaches that it was a surprising result of the present invention that the MMP inhibitors can inhibit MMP, even in the conjugate form. One of ordinary skill in the art reading Gallardy would not have a reasonable expectation that the MMP

inhibitors will retain their activity even after being conjugated. Thus, it would not be obvious to substitute the MMP inhibitors of Gallardy for the prednisolone of Akima or the ibuprofen of Prestwich.

The disclosure in Prestwich at column 14, lines 27-51, for use against joint disease, suggests that the purpose of coupling the HA, which is recognized as having its own effect against arthritis, with an antiinflammatory, such as ibuprofen or hydrocortisone, is to serve as a sustained release agent. It states that the therapeutic agent is released by chemical, enzymatic and physical erosion of the hydrogel and/or the covalent HA-drug linkage over a period of time (column 14, lines 31-35). The presently claimed invention however has surprisingly shown that the therapeutic agent does not have to be released in order to have its effect. Thus, the conjugate recited in the present claims will have its effect while still in conjugate form and therefore the purpose of the present invention is retainability for continuous effect even without release of the therapeutic agent.

For the reasons presented in this supplemental amendment and in the amendment filed December 6, 2005, one of ordinary skill in the art reading the disclosures and

teachings of Prestwich, Akima and Gallardy cannot be led to the presently claimed invention.

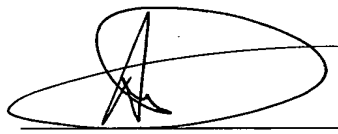
Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance.

Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By 
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YUAS\Tamura5\PTO\supplemental amendment.doc